Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

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Adolescents and Young Adults with HIV (Last updated December 18, 2019; last reviewed December 18, 2019)

Key Considerations and Recommendations

- Adolescents living with HIV largely belong to two distinct groups—those who acquired HIV in infancy and are heavily antiretroviral therapy (ART)-experienced, and those who acquired HIV more recently during their teens.
- ART is recommended for all individuals with HIV **(AI)** to reduce morbidity and mortality and to prevent HIV transmission. Therefore, ART is also recommended for ART-naive adolescents.
- Before initiation of therapy, adolescents' readiness and ability to adhere to therapy within their psychosocial context need to be carefully considered as part of therapeutic decision making **(AIII)**.
- Once ART is initiated, appropriate support is essential to reduce potential barriers to adherence and maximize the likelihood of achieving sustained viral suppression **(AII)**.
- Data from an observational study in Botswana suggest that there may be an increased risk of neural tube defects in infants born to individuals who were receiving dolutegravir at the time of conception. Before initiating an integrase strand transfer inhibitor-based regimen in an adolescent of childbearing potential, clinicians should review Table 6b for information to consider when choosing an ART regimen.
- The adolescent sexual maturity rating (SMR) can help guide regimen selection when initiating or changing an ART regimen as recommended by either the Adult and Adolescent Antiretroviral Guidelines or the Pediatric Antiretroviral Guidelines. The Adult and Adolescent Aniretroviral Guidelines are more appropriate for postpubertal adolescents (i.e., those with SMRs of 4 or 5) **(AIII)**.
- Pediatric and adolescent care providers should prepare adolescents for the transition into adult care settings. Adult providers should be sensitive to the challenges associated with such transitions, consulting and collaborating with adolescent HIV care providers to ensure adolescents' successful transition and continued engagement in care **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Older children and adolescents now make up the largest percentage of children with HIV who receive care at pediatric HIV clinics in the United States. The Centers for Disease Control and Prevention (CDC) estimates that 26% of the approximately 50,000 people with newly diagnosed HIV in 2010 were youth 13 to 24 years of age. In this age group, 57% of the infections were among young black/African Americans and 75% were among young men who have sex with men (MSM).[1] Among youth living with HIV in 2010, CDC estimates that almost 60% had undiagnosed infections and were unaware they had HIV.[1] Trends in HIV/AIDS prevalence indicate that the disproportionate burden of HIV among racial minorities is even greater among minority youth aged 13 to 24 years than among those older than 24 years.[2] Furthermore, trends for all HIV diagnoses among adolescents and young adults decreased or remained stable for all transmission categories except among young MSM in 46 states and five U.S.-dependent areas from 2007 to 2010. Adolescents with HIV represent a heterogeneous group in terms of socio-demographics, mode of HIV acquisition, sexual and substance abuse history, clinical and immunologic status, psychosocial development, and readiness to adhere to medications. Many of these factors may influence decisions concerning when to start antiretroviral therapy (ART) and what antiretroviral (ARV) medications to use.

Most adolescents who acquire HIV do so through sex. Many of them have recently acquired HIV and are unaware of their HIV status. Many are in an early stage of HIV infection, which makes them ideal candidates for early interventions, such as prevention counseling, linkage to and engagement in care, and initiation of ART.[3] High-grade viremia was reported in a cohort of youth living with HIV who were identified by adolescent HIV specialty clinics in 15 major metropolitan U.S. cities. The mean HIV viral load for the cohort was 94,398 copies/mL; 30% of the youth were not successfully linked to care.[4] In a study of youths with

recent HIV infection, as determined by the detuned antibody testing assay strategy, which defined recent infection as occurring within 180 days of testing, primary genotypic resistance mutations were reported in 18% of the youths.[5] In an ARV treatment trial, a cohort of ART-naive youth who had behaviorally acquired HIV showed substantial multiclass resistance.[6] As these youth were naive to all ARV drugs, these results reflect transmission of resistant virus. This transmission dynamic indicates that a substantial proportion of the study participants' sexual partners were likely to be older and ART-experienced; thus, it is imperative that clinicians use baseline resistance testing to guide initial therapy in youth who have recently acquired HIV and who are naive to ART.

A limited but increasing number of adolescents with HIV are long-term survivors of HIV that was acquired perinatally or in infancy through blood products. These adolescents are usually heavily ART-experienced and may have a unique clinical course that differs from that of adolescents who acquire HIV later in life.[7] Adolescents who acquired HIV perinatally or in infancy often initiated ART early in life with mono- or dual-therapy regimens, resulting in incomplete viral suppression and emergence of viral resistance. If these heavily ART-experienced adolescents harbor resistant virus, optimal ARV regimens should be selected using the same guiding principles used for heavily ART-experienced adults (see Virologic Failure).

Developmentally, adolescents are at a difficult crossroad. Their needs for autonomy and independence and their evolving decisional capacity compete with their concrete thinking processes, risk-taking behaviors, preoccupation with self-image, and need to fit in with their peers. This makes it challenging to sustain adolescents' focus on maintaining their health, particularly for those with chronic illnesses. These challenges are not specific to any particular transmission mode or stage of disease. Thus, irrespective of disease duration or mode of HIV transmission, every effort must be made to engage and retain adolescents in care so they can improve and maintain their health for the long term.

Given the challenges of retaining youth in care and achieving long-term viral suppression,[8] more intensive case management approaches may be considered for adolescents with HIV.[9,10] Adolescents may seek care in several settings, including pediatric-focused HIV clinics, adolescent/young adult clinics, and adult-focused clinics.[11] When available, youth services may help enhance HIV care engagement and retention among adolescents.[12] Regardless of the setting, expertise in caring for adolescents is critical to creating a supportive environment for engaging youth in care.[11]

Antiretroviral Therapy Considerations in Adolescents

The START and TEMPRANO trials are discussed elsewhere in these guidelines (see Initiation of Antiretroviral Therapy).[13,14] The results of these trials supported the initiation of ART in all individuals who are able and willing to commit to treatment, and who can understand the benefits and risks of therapy and the importance of excellent adherence.[13,14] Neither of these trials included adolescents; however, the recommendations that were developed using the data from these trials apply to adolescent patients as well as adult patients. Adolescents are expected to derive benefits from early ART initiation that are similar to those observed in adults. Given the psychosocial turmoil that may occur frequently in the lives of American youth with HIV, their ability to adhere to therapy needs to be carefully considered as part of therapeutic decision making. Once ART is initiated, appropriate support is essential to reduce potential barriers to adherence and maximize the likelihood of achieving sustained viral suppression.

The adolescent sexual maturity rating (SMR; also known as the Tanner stage) can be helpful when ART initiation is being considered for this population (see this SMR table from the World Health Organization). Adult guidelines for ART initiation (see What to Start) or regimen changes are usually appropriate for postpubertal adolescents (SMR 4 or 5) because the clinical course of HIV infection in postpubertal adolescents who acquired HIV sexually or through injection drug use during adolescence is more similar to that in adults than that in children. Adult guidelines can also be useful for postpubertal youth who acquired HIV perinatally and whose long-term HIV infection has not affected their sexual maturity (SMR 4 or 5).

Pediatric guidelines for ART may be more appropriate for adolescents who acquired HIV during their teen years (e.g., through sex) but who are sexually immature (SMR 3 or less), and for adolescents who acquired HIV perinatally with stunted sexual maturation (i.e., delayed puberty) from long-standing HIV infection or other comorbidities (SMR 3 or less; see What to Start in the Pediatric Antiretroviral Guidelines).

Postpubertal youth who acquired HIV perinatally often have treatment challenges associated with the long-term use of ART that mirror those of ART-experienced adults, such as extensive resistance, complex regimens, and adverse drug effects (see Virologic Failure, Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression, and Adverse Effects of Antiretroviral Agents). Postpubertal adolescents who acquired HIV perinatally may also have comorbid cognitive impairments that compound adherence challenges that are common among youth.[15]

Dose of ARV drugs should be prescribed according to the patient's SMR and not solely based on age. Adolescents in early puberty (SMR 3 or less) should be administered doses on pediatric schedules, whereas those in late puberty (SMR 4 or 5) should follow adult dosing schedules. However, SMR and age are not necessarily directly predictive of drug pharmacokinetics (PKs). Because puberty may be delayed in children with perinatally acquired HIV,[16] continued use of pediatric doses in puberty-delayed adolescents can result in medication doses that are higher than the usual adult doses. Data are lacking on the optimal doses for each ARV drug for this group of children; therefore, issues such as toxicity, pill or liquid volume burden, adherence, and virologic and immunologic parameters should be considered when determining when to transition youth from pediatric to adult doses. Youth who are in their growth spurt period (i.e., SMR 3 in females and SMR 4 in males) and who are following adult or pediatric dosing guidelines and adolescents who have transitioned from pediatric to adult doses should be closely monitored for medication efficacy and toxicity. Therapeutic drug monitoring can be considered in these circumstances to help guide therapy decisions. PK studies of drugs in youth are needed to better define appropriate dosing. For a more detailed discussion, see the Pediatric Antiretroviral Guidelines.

Preliminary data from a study in Botswana reported an increased prevalence of neural tube defects (NTDs) among infants born to women who were receiving dolutegravir (DTG) at the time of conception; the prevalence of NTDs in these infants was found to be 0.9%.[17,18] Follow-up data showed that the prevalence of NTDs in infants who had been exposed to DTG at conception was lower than originally reported (0.3%), but still higher than the prevalence in infants who were exposed to ARV regimens that did not contain DTG (0.1%).[19,20] There are insufficient safety data on the use of bictegravir (BIC) at the time of conception and during pregnancy to determine whether it is safe to use. An approach similar to that outlined for DTG should be considered for BIC-containing ART **(AIII)**. Before initiating an integrase strand transfer inhibitor-based regimen in an adolescent of childbearing potential, clinicians should review the information in Table 6b.

Clinicians should refer to the Perinatal Guidelines for information on the safety and efficacy of ARV use in pregnancy.

Adherence Concerns in Adolescents

Adolescents with HIV are especially vulnerable to specific adherence problems because of their psychosocial and cognitive developmental trajectory. To meet the medical and psychosocial needs of adolescents with HIV, who frequently lack both health insurance and experience with health care systems, comprehensive systems of care are required. Studies of adolescents who acquired HIV during their teen years and adolescents with perinatal acquisition demonstrate that many adolescents in both groups face numerous barriers to adherence.[21-23] Compared with adults, these youth have lower rates of viral suppression and higher rates of virologic rebound and loss to follow up.[24] Reasons that adolescents with HIV often have difficulty adhering to medical regimens include the following:

- Denial and fear of their HIV diagnosis;

- Misinformation;
- Distrust of the medical establishment;
- Fear of ART and lack of confidence in the effectiveness of medications;
- Low self-esteem;
- Unstructured and chaotic lifestyles;
- Mood disorders and other mental illness;
- Lack of familial and social support;
- Lack of or inconsistent access to care or health insurance; *and*
- Risk of inadvertent disclosure of their HIV status if parental health insurance is used.

Clinicians selecting treatment regimens for adolescents must balance the goal of prescribing a maximally potent ART regimen with a realistic assessment of existing and potential support systems to facilitate adherence. Adolescents benefit from reminder systems (e.g., apps, timers, and pill boxes) that are stylish and/or inconspicuous.[25] In a randomized controlled study among nonadherent youth aged 15 years to 24 years, youth who received medication reminders through their cell phones demonstrated significantly better adherence and lower viral loads than youth who did not receive the reminder calls.[26] It is important to make medication adherence user-friendly and to avoid HIV-related stigma as much as possible for the older child or adolescent. Adolescents may not understand the importance of taking medications when they are asymptomatic, particularly when the medications have side effects. Adherence to complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers.[27-29] Directly observed therapy may be considered for some adolescents with HIV, such as those with mental illness.[30-34]

Difficult Adherence Problems

Predicting long-term adherence in an adolescent can be very challenging because adolescence is characterized by rapid changes in physical maturation, cognitive processes, and life style. A young person's ability to adhere to therapy needs to be considered as part of therapeutic decision-making. Erratic adherence may result in the development of resistance mutations, which can limit future regimen options. Clinicians who care for adolescents with HIV frequently manage youth who pose significant concerns regarding their ability to adhere to therapy. In these cases, the following strategies can be considered:

- A short-term deferral of ART until adherence is more likely or while adherence-related problems are aggressively addressed;
- An adherence testing period in which a placebo (e.g., vitamin pill) is administered; *and*
- The avoidance of any regimens with low resistance barriers.

Such decisions should ideally be individualized to reflect each patient's clinical status. For a more detailed discussion on specific therapy and adherence issues for adolescents with HIV, see Adherence to the Continuum of Care and the Pediatric Antiretroviral Guidelines.

Other Considerations in Adolescents

All adolescents should be screened for sexually transmitted infections (STIs), especially human papilloma virus (HPV). In young MSM, screening for STIs may require sampling from several body sites because oropharyngeal, rectal, and urethral infections may be present in this population.[35] For a more detailed discussion on STIs, see the most recent CDC guidelines,[36] the Adult and Adolescent Opportunistic Infection Guidelines, and the Pediatric Opportunistic Infection Guidelines on HPV among adolescents with HIV.

Family planning counseling, including a discussion of the risks of perinatal HIV transmission and methods to reduce those risks, should be provided to all youth. Providing gynecologic care for female adolescents with

HIV is especially important. Choice of ART may also be affected by a patient's potential for pregnancy and choice of contraception, since some ARV drugs can interact with hormonal contraceptives (see Drug-Drug Interactions).

Finally, transgender youth with HIV represent an important population that requires additional psychosocial and health care considerations. For a more detailed discussion, see Adolescent Trials Network Transgender Youth Resources.

Transitioning Care

HIV is a lifelong infection that requires treatment through several stages of growth and development; therefore, HIV care programs and providers need to be flexibile in order to appropriately transition care for children, adolescents, and young adults with HIV. A successful transition requires an awareness of the fundamental differences between many adolescent and adult HIV care models.

In most adolescent HIV clinics, care is more teen-centered and multidisciplinary, with primary care highly integrated into HIV care. Teen services, such as sexual and reproductive health, substance abuse treatment, mental health, treatment education, and adherence counseling are all found in one clinic setting. In contrast, some adult HIV clinics may rely more on referring the patient to separate subspecialty care settings, such as gynecology. Transitioning the care of an emerging young adult includes considering areas such as access to medical insurance; the adolescent's degree of independence/autonomy and decisional capacity; patient confidentiality; and informed consent. Also, adult clinic settings tend to be larger and can easily intimidate younger, less-motivated patients.

As an additional complication to this transition, adolescents with HIV belong to two epidemiologically distinct subgroups with unique biomedical and psychosocial needs:

- Adolescents who acquired HIV perinatally. These adolescents are likely to have longer histories of disease burden, complications, and chronicity; less functional autonomy; a greater need for ART; and higher mortality risks.
- Youth who more recently acquired HIV during their adolescence. These adolescents are likely to be in earlier stages of HIV infection and have higher CD4 T lymphocyte cell counts; they are also less likely to have drug resistance mutations and may benefit from simpler treatment regimens.

Interventions to facilitate transition should be implemented early to ensure a successful transition.[37] These interventions include the following:

- Developing an individualized transition plan to address comprehensive care needs, including medical, psychosocial, and financial aspects of transitioning;
- Optimizing provider communication between adolescent clinics and adult clinics;
- Identifying adult care providers who are willing to care for adolescents and young adults;
- Addressing patient and family resistance to transition of care caused by lack of information, concerns about stigma or risk of disclosure, and differences in practice styles;
- Helping youth develop life skills, including counseling them on the appropriate use of a primary care provider and how to manage appointments; the importance of prompt symptom recognition and reporting; and the importance of self-efficacy in managing medications, insurance, and assistance benefits;
- Identifying an optimal clinic model based on specific needs (i.e., simultaneous transition of mental health and/or case management versus a gradual phase-in);
- Implementing ongoing evaluation to measure the success of a selected clinic model;
- Engaging adult and adolescent care providers in regular multidisciplinary case conferences;
- Implementing interventions that may improve outcomes, such as support groups and mental health

consultation;

- Incorporating a family planning component into clinical care; *and*
- Educating HIV care teams and staff about transitioning.

Discussions regarding transition should begin early, before the actual transition process.[38] Attention to the key interventions noted above will likely improve adherence to appointments and allow the youth to be retained in care.

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